

aptamers; peptide nucleic acid molecules; peptides; and affinity resins which recognize DNA having a particular G+C content or methylation status,

under conditions which permit specific binding, wherein said sample comprises a subset of nucleic acid molecules having a sequence that binds to said sequence-specific binding activity, and wherein a bound subset of nucleic acid molecules is retained by the sequence-specific binding activity, such that the subset of bound nucleic acid molecules is enriched for molecules comprising the sequence recognized by the sequence specific binding activity; and

b) detecting a sequence difference with respect to a reference sequence in the subset of nucleic acid molecules,

wherein steps (a) and (b) enrich for and identify a nucleic acid sequence difference with respect to a reference sequence.

57. (Three times amended) A method of enriching for and identifying nucleic acid sequence differences with respect to a reference sequence comprising:

- a) fragmenting a nucleic acid sample from one or more individuals;
- b) physically separating a subset of said nucleic acid fragments based on the size of the fragments;
- c) operatively linking a fragment created in step (a) or said subset of step (b) with an oligonucleotide or a vector;
- d) replicating said operatively linked subset to form an enriched collection of replicated molecules; and
- e) detecting one or more nucleotide sequence differences in the members of said collection of step (d) by DNA sequencing,

wherein said steps (b) and (c) follow step (a) but can occur in either order, followed thereafter by steps (d) and (e) in that order, wherein said steps (a)-(e) enrich for and identify a nucleic acid sequence difference with respect to a reference sequence.

69. (Three times amended) A method of enriching for and identifying nucleic acid sequence differences with respect to a reference sequence comprising: